Managing Risk to Quality: *The Good and the Bad*

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Introduction to Managing Risk

NOTE: Opening story; When I was working in industry,

I had the opportunity to be a new plant manager.

One day my boss asked me how I was managing risk.

Up to then In all my previous positions I was managing the production schedule, making sure materials were available, and making sure employees followed their batch records.

I said, I was not managing risk. I managed the schedules, employee safety, and met performance goals.

My boss laughed when he heard this and asked me to come back in a week and tell him how my plant was managing risk

I assembled my staff and we came up with a list

My boss looked at the list and said “these are quality and safety metrics but they do not tell me how you are managing risk”.

He had me go back again and I called up one of my former professors and he gave me 3 quotes to contemplate.

Three Quotes to Consider

"Risk is like fire: If controlled it will help you; if uncontrolled it will rise up and destroy you."

—*Theodore Roosevelt*, the 26th President of the United States

"Risk Management is about people and processes and not about models and technology."

—*Trevor Levine,* founder or Riskczar Corporation

Three Quotes to Consider (continued)

"The first step in the risk management process is to acknowledge the reality of risk. Denial is a common tactic that substitutes deliberate ignorance for thoughtful planning."
—*Charles Tremper* , is the former executive director Nonprofits' Risk Management and Insurance Institute

Signals of Quality Drift

- Significant audit findings

NOTE:

Why am I speaking about risk management?

Because quality matters and our industry has not had an exemplary record.

Let's look at some quality drift signals.

2015 Top Observations

- 211.22(d): Quality Unit responsibilities
- 211.160(b): Laboratory controls
- 211.192: Investigation failures
- 211.113(b): Microbiological controls
- 211.100(a): Production process
- 211.42(c)(10)(iv): Environmental monitoring
- 211.68(a): Electronic equipment controls

NOTE: FDA inspectional records from FACTS database.

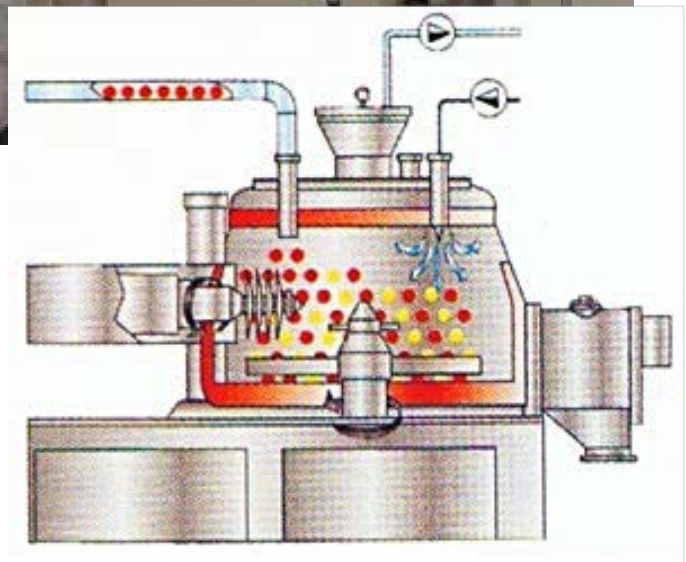
Risk Reduction is Hard Work

- Are you really using risk management effectively?
- Lets look at three examples
  - "The major difference between a thing that might go wrong and a thing that cannot possibly go wrong is that when a thing that cannot possibly go wrong goes wrong it usually turns out to be impossible to get at or repair."
    —*Douglas Adams,* English humorist and science fiction novelist (1952 – 2001)

NOTE:

- Multidisciplinary work
- Requires expert facilitation
- You need effective critics
- Absolute honesty is required in assessments

Tablet Blend Uniformity Example



- Formulation
- Process technology

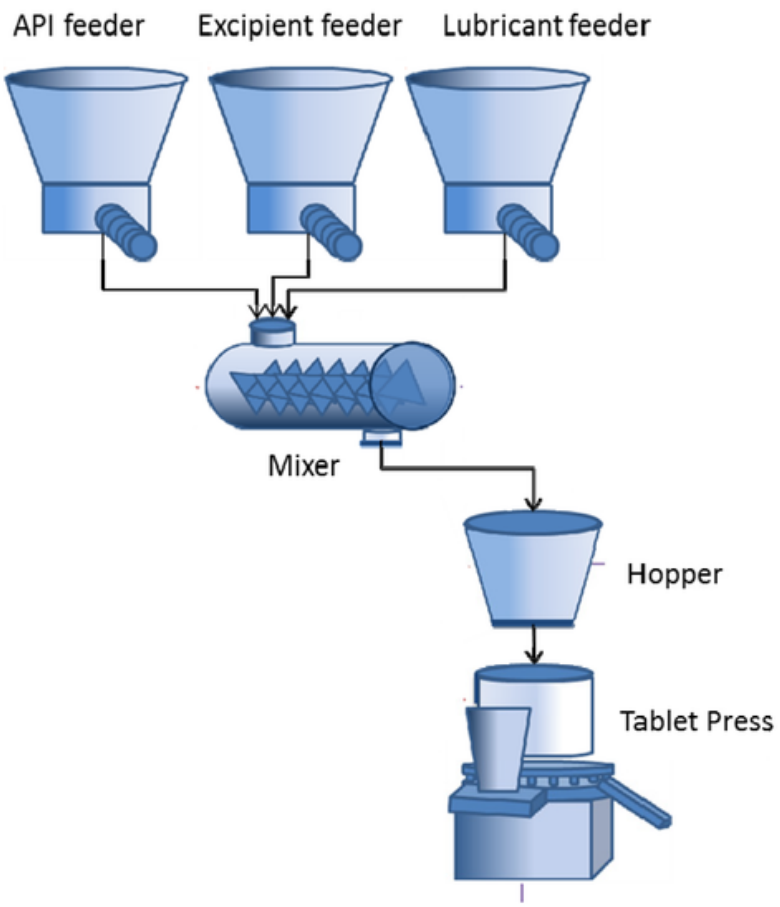
NOTE: Formulation example:

Discuss dry mix, wet granulation, continuous process.

Process Technology example:

Discuss PAT online in Blender, NIR in process stream and end point determination, and Raman in line sensors.

Example of Continuous Process

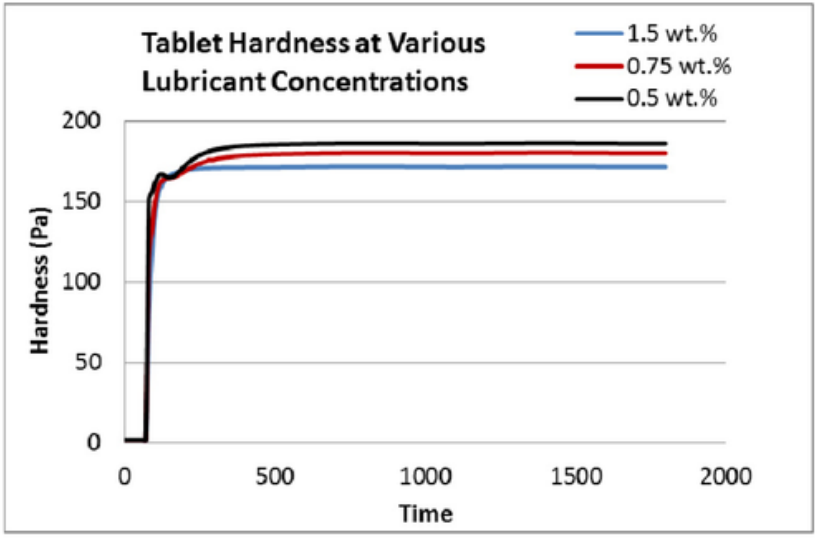


NOTE: What risks can be avoided by this process?

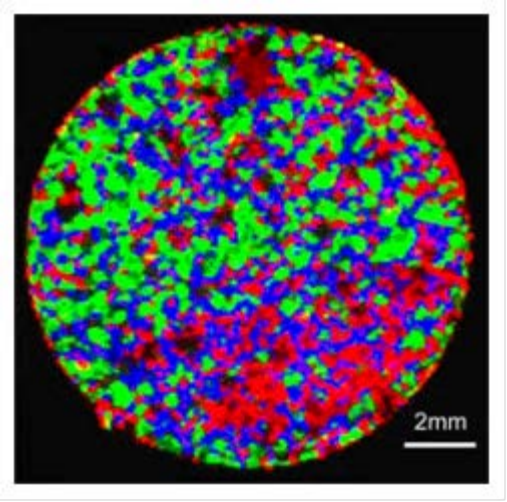
Eliminates blending and storage in drums before tableting.

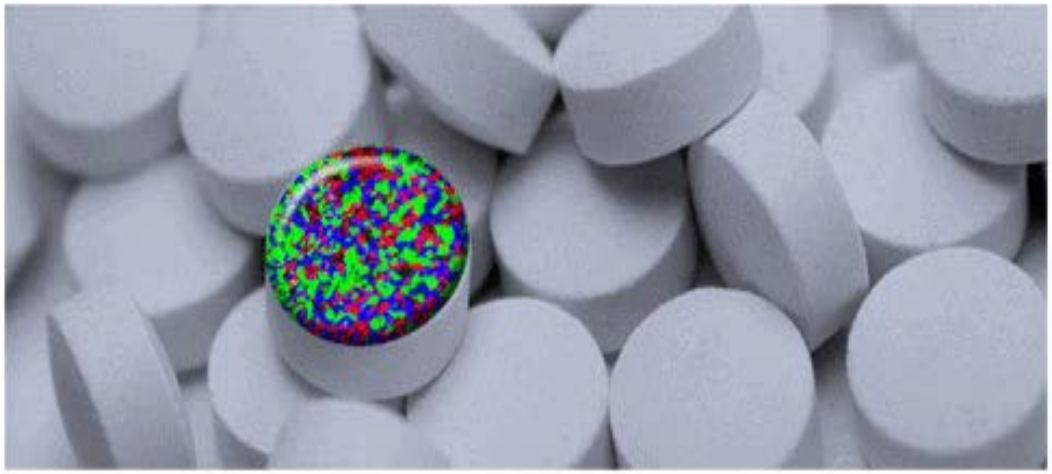
In-line tablet assay has feedback loop to component feeders to adjust concentration of API.

Need to control weight feeders very precisely for low dose API.



These are Typical Results





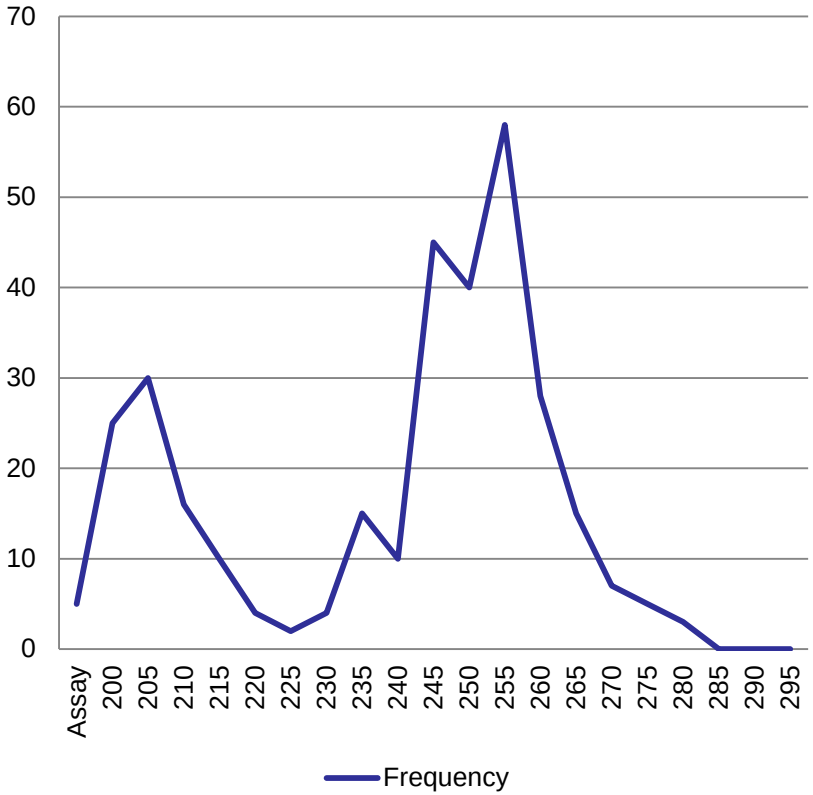
These are Raman spectral images of the surface of tablets from different processes.

Tablet on left is not very uniform from a direct compression process.

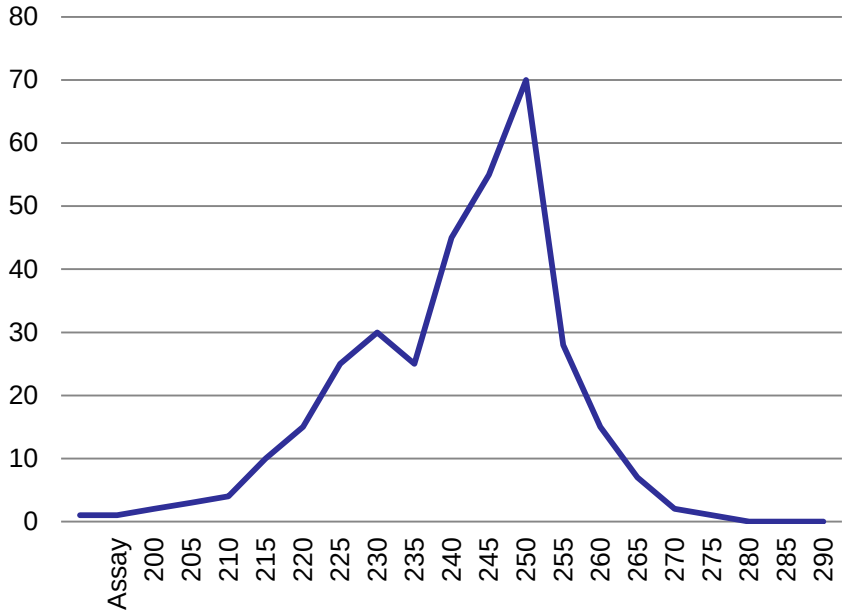
The example on the right is a tablet with better dosage uniformity produced from a continuous process.

Results from Our Process Changes

Direct Blend



Wet Granulation Process



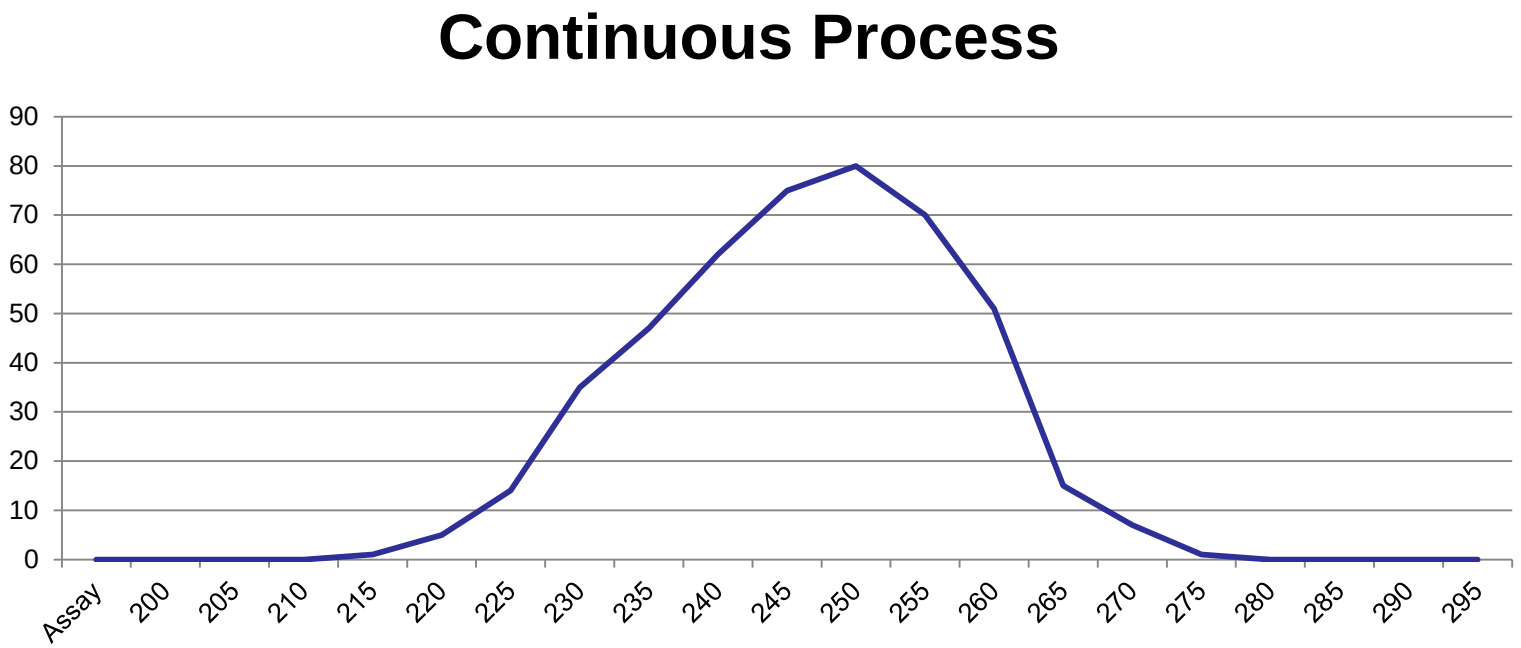
NOTE: What the research found when we examined CU for tablets from the different processes:

Bimodal CU which was traced to demixing in the tablet hopper.

Wet granulation produced better results but still did not have tight distribution and the shoulder still indicated we had some segregation going on.

Representative of actual test data

Results from Our Process Changes
(continued)



NOTE: This is an example of the final process CU sample distribution for the continuous manufacturing process.

So which process would reduce process risk?

Each process has its own risk characteristics that need to be evaluated when you are designing a drug product.

If you never examine and determine the process characteristics you can have a marginal process that results in high rejects, failed batches, and/or customer adverse events.

Sterile Process Risk Example

- Look at microbiological risk
- Look at personnel intrusion risks

NOTE: Now we will look at three examples of aseptic processing and look at process optimization practices with personnel and their effect upon microbiologic contamination risk. Even today sterility assurance failures are near the top issues with FDA 483 observations and product recalls.

Higher Risk to Moderate Risk

NOTE: Picture on the left is a conventional filling line with unidirectional air supply.

What are the human interactions with this filling line?

Briefly discuss movement of personnel into the unidirectional air stream to take samples, pick up vials, and take in-process samples, perform line set-ups, and cleaning.

The picture on the right is a RABS filling line that has glove ports that minimizes some human interaction with filling line.

Doors can still be opened. There are better safeguards but still vulnerabilities that need to be addressed by SOP (e.g., pin holes in gloves).

Lowest risk

NOTE: What do you see different in this picture?

No glove ports and no doors that can be easily opened.

Does this provide better product protection?

Line has automation of changeover process, clean in place technology, auto sampling, in-process controls.

This provides increase operator safety and increased efficiency as additional benefits of a lower risk process

Batch Record Example

- Paper Batch Records
- Electronic Batch Record (EBR)
  - Bad EBR example
  - Good EBR example

NOTE: The last example which is perhaps the most important that illustrates the impact of risk reduction is how a simple batch record can be transformed into a useful management tool that improves the quality of the work, reduces the risk of an error, and improves the quality of the drug products manufactured.

People are part of the process and in many cases they are overlooked as important aspects of a risk reduction strategy.

Risk Factors

- Hard to follow
- Errors in data entry
- Mistakes by people
- Missing pages
- Missing documents

Company name

Batch production record in accordance with batch production record 0024-01

Drago solution Batch description: **9909205**

0.025 mg per dosage in 4.5 ml cartridges

1.B Implementation

Calibrate the balance.Then weigh the following starting materials according to SOP... Label the weighed starting materials in accordance with SOP...

Calibrating the balance

Equipment designation	Inventory no.	Result Calibration	Processor Check
600 kg floor balance	96940		P: C:
			P: C:

Date of initial weigh-in:

Starting material	Batch no.	Inv. no. Balance	Initial weigh-in Target [g]	Tolerance range [g]	Initial weigh-in Actual [g]	Processor Check
Active pharmaceutical in			181,00	180,91 - 181,09		P: C:
Purified water			9419,00	9414,29 - 9423,71		P: C:
Sodium edetate			0,8000	0,7996 0,8004		P: C:
Ethanolum anhydricum			56600,00	56571,70 - 56628,30		P: C:
Citric acid*			q.s.	q.s.		P: C:
Total mass			ad 66200	ad 66200		P: C:

Comments:

Conclusion of processing step **WEIGH-IN**

Signature: Date/processor Date/check

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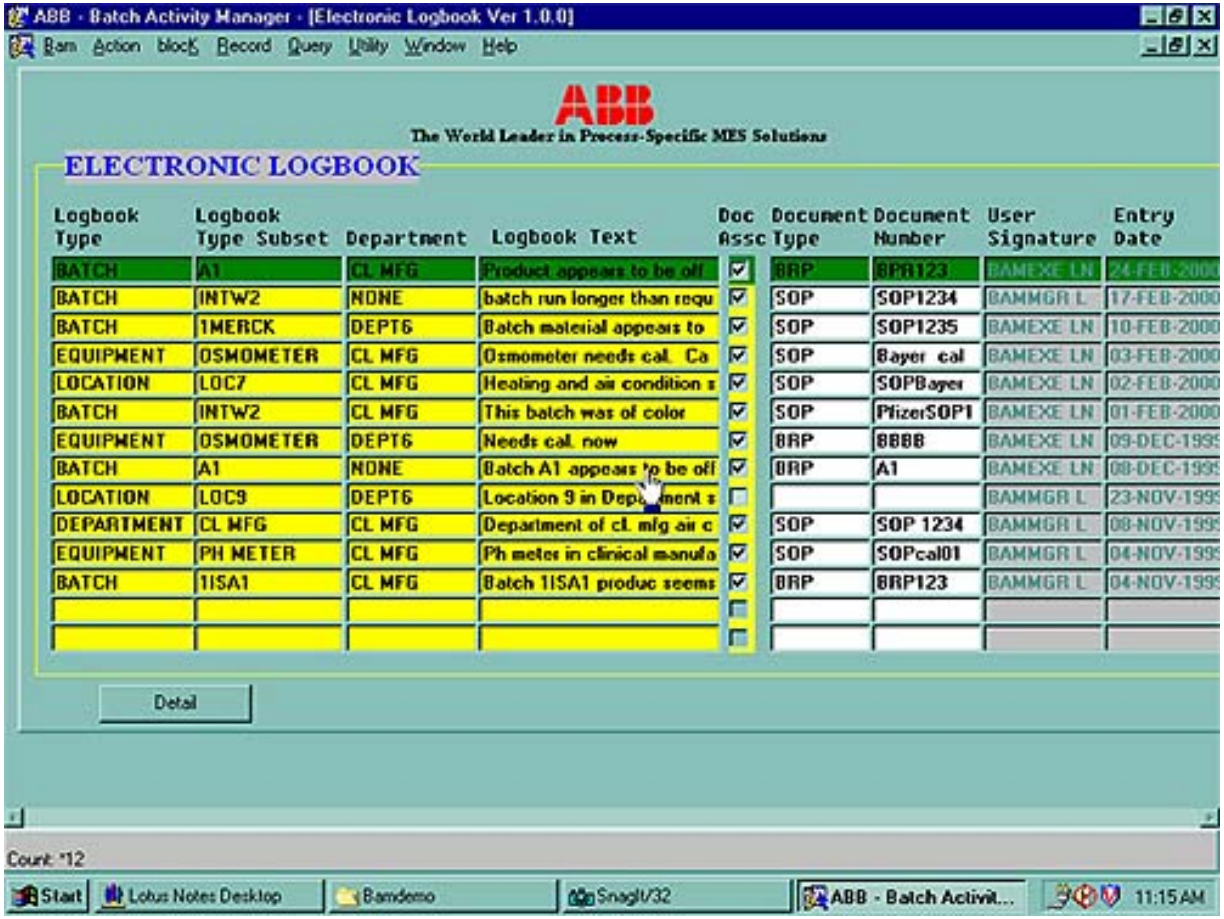
NOTE: Many SOPs and batch records are written by scientists with little training on human factor design and risk minimization techniques.

Sometimes batch records themselves need an SOP on how to fill out a batch record or the sequence of operations is totally missing.

At one facility, I asked how factor workers were trained on using a batch record and the answer I received is that a new employee could not pick up a batch record and follow it to make a batch. The new employee needed to be taught by an experienced employee before they could make a batch on their own. Do you think that this process is really under control or reduces risk?

Even if they are well designed, batch records still rely upon people to fill them out and errors can occur.

Much Like Paper Batch Records



NOTE: This is an example of a electronic batch record that was a good idea but lacked any use of risk mitigation strategies.

All the firm did was copy the manual batch record and make an electronic version of it.

It still had poor logical flow, required extensive training, and did not prevent errors.

Work Activity Based System

NOTE: This is an example of a weighing process step that was automated.

It is an improvement of the previous electronic batch record but only addresses some of the human factor risks.

It is linked to a weighing scale which records the data from the weighing process, but it still relies upon manual data entry of ingredients, component codes, and batch numbers. It was not linked to the entire manufacturing process.

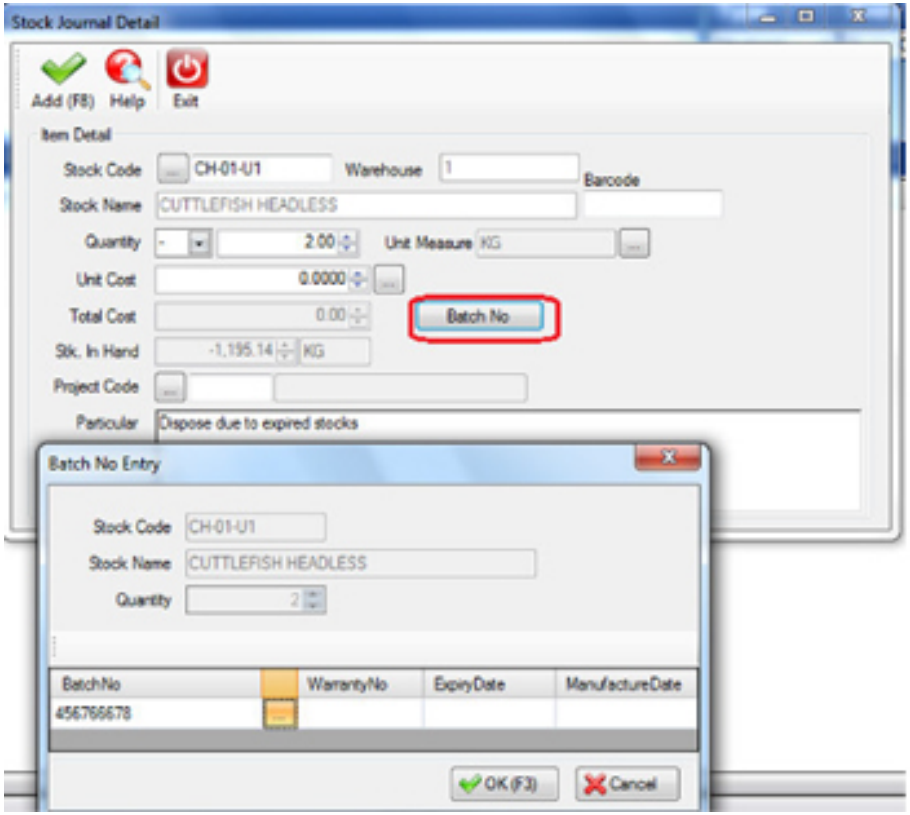
Major Change in Human Interaction

NOTE: Recently there has been a shift in focus to better human interaction with manufacturing processes and batch documentation.

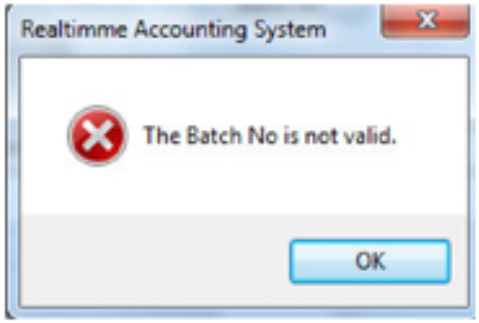
Information is now at the finger tip of each and every employee and batch processes can be monitored in real time.

Properly designed systems enhance product quality, reduce employee errors, and in some cases have eliminated employee errors if properly validated.

Error Checking



System built-in self checking if batch number do not exists

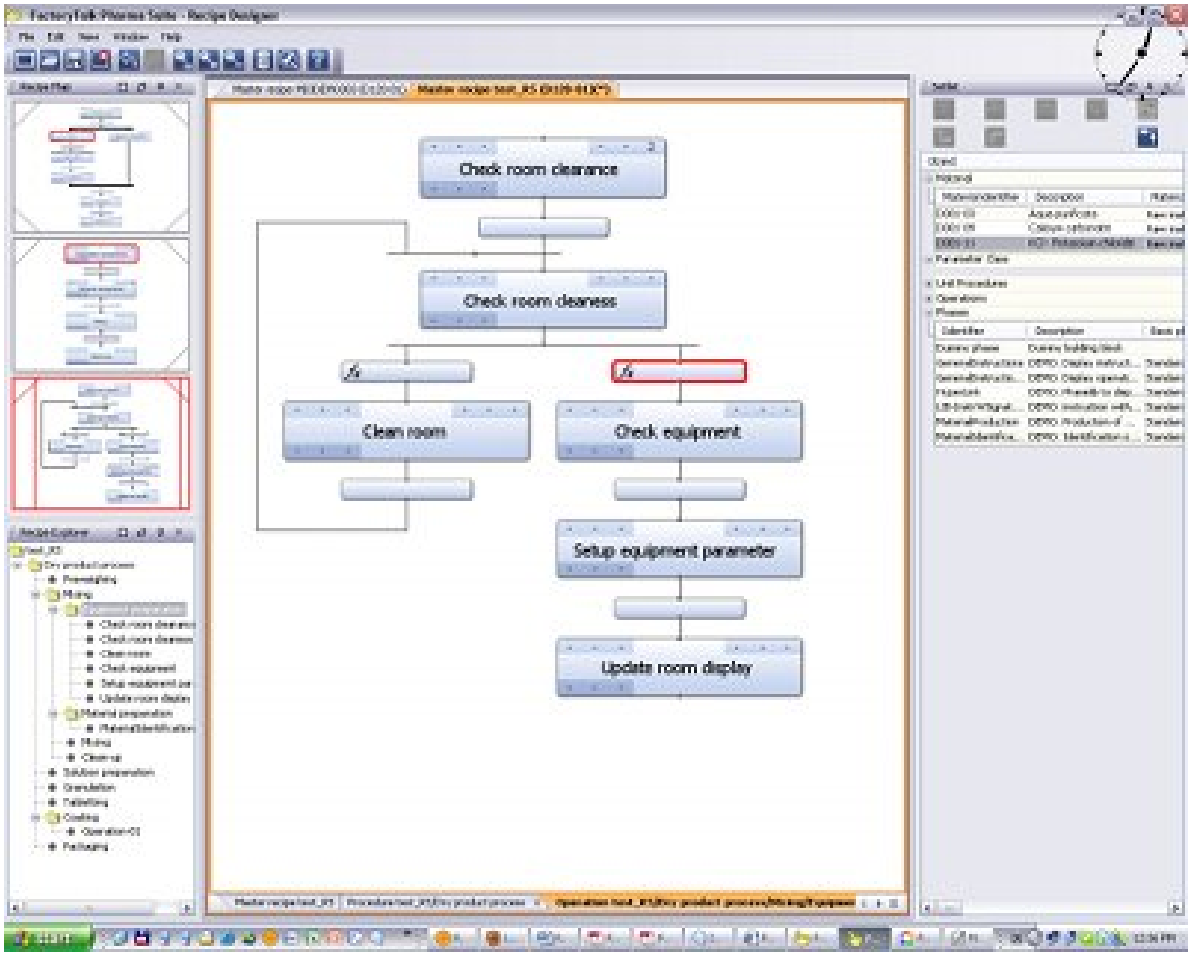


NOTE: Error checking in these systems are designed with foresight and use of “what if” analysis to design safeguards that will minimize risk.

Discuss example.

Even in the laboratory electronic documentation records are being implemented and can control the risk of data integrity problems.

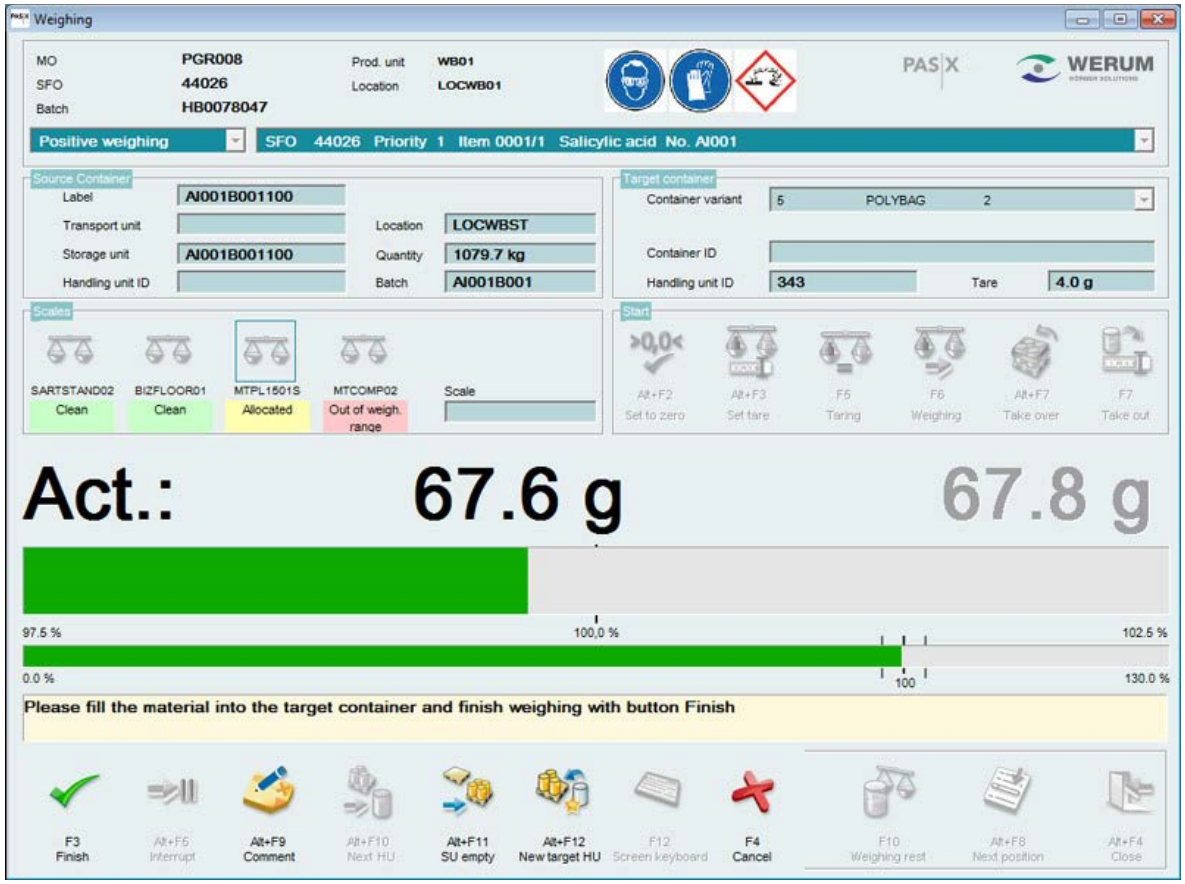
Logical Process Control



NOTE: This example of an electronic batch record uses logical process flow graphics to easily guide an employee thru a manufacturing process.

It also has sophisticated real time monitoring and highlights processes that are in an alarm condition that will then allow employees to rapidly react to errors. Some of these systems can automatically adjust process parameters to compensate for changes and process drift. They take a lot of time to design but the results are improved product quality and reduced risk.

Another Example of Improved Human Interface with a Process



NOTE: This is another example of improved human interface with a process where the electronic batch record is providing more than one cue for the employee to perform a weighing operation. Some of these systems now use auditory, color change, and print to convey information to an employee. This type of design compensates for differences in humans and their ability to interpret the information being displayed.

What risks do you think this minimizes?

A. Real time results, automatic documentation of all components used, reduces risk of data manipulation

Effective Real Time Management

NOTE: Modern electronic batch records also allow real time monitoring and multiple eyes on the same process.

What controls do you think are working in this type of system?

Automated computer controls

Supervisor observation

In field communication

Process trending

Redundant controls do minimize process risk and improve drug product quality.

If one control fails another control will work.

Impact of Effectively Managing Risk

- Reduces process errors
- Reduces employee errors
- Reduces rejects and scrap
- Reduces need for investigations
- Reduces FDA 483 observations
- Reduces recalls
- Improves drug product quality

Summary

"Risk comes from not knowing what you're doing."

—*Warren Buffet*

Acknowledgements

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